REMARKS

Petition Decision

On September 3, 2009 the USPTO mailed a decision on Petition, granting the Petition filed on July 20, 2009 and supplemented on August 10, 2009 by Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften E.V. (Max-Planck) requesting revocation of power of attorney and waiver of the requirement of 37 CFR 1.32 (b)(4) for appointment of power of attorney by less than all of the applicants or owners. The USPTO has indicated that all further correspondence must be signed by both a registered practitioner representing Max-Planck (Rothwell, Figg) and a registered practitioner representing the interests of the other co-assignees and concludes that the "Technology Center is advised that communications filed on or after the mailing date of this decision not signed in accordance with this decision must also be regarded as informal, and as such, to take the action it deems appropriate."

This amendment in response to Office Action of March 9, 2009 is filed without the co-signature of attorney for Max-Planck. In a letter dated March 8, 2009 Robert Murray of Rothwell, Figg has indicated that Max-Planck is unwilling to co-sign the amendment (a copy of the letter is attached as Exhibit A). Max-Planck has a contractual obligation under two contracts in which it agreed that Whitehead Institute for Biomedical Research (Whitehead) "shall manage" and have "primary responsibility" for the "patent filing, prosecution and maintenance of the [Tuschl I invention] applications." (copies of contracts are attached to Whitehead's response in opposition to Petition filed on July 31, 2009). Whitehead has the sole authority to make decisions regarding the prosecution of the application pursuant to the contract. To the extent that the USPTO's decision on Petition precludes Whitehead from making decisions regarding the prosecution of the application, it is unlawful and should be reversed. At a minimum and in order to prevent irreparable harm, Whitehead should be permitted to preserve the status quo by submitting the instant amendment in response to Office Action without the co-signature of representatives of Max-Planck. The USPTO should accept the amendment and the payment of a fee for a three month extension of time for at least the limited purpose of avoiding abandonment of the application until the District Court enters a final judgment in the pending litigation.

Judge Saris of the United States District Court issued a Memorandum and Order on September 1, 2009 in Civil Action 09-11116-PBS denying Max-Planck's request for Preliminary Injunction (copy attached to IDS filed on September 3, 2009). In the Memorandum and Order, Judge Saris held that Max-Planck did not demonstrate a likelihood of success on the merits in establishing that Max-Planck had the authority to direct Whitehead to take certain actions regarding prosecution of the Tuschl I patent applications. Specifically, Judge Saris stated: "[t]he agreements do not give Max-Planck veto power over Whitehead's decisions in prosecuting the patent so long as the decisions are in good faith, as these appear to have been." Memo. at page 16. By granting Max-Planck's Petition, the USPTO has permitted Max-Planck to effectively block prosecution of the application.

Claim Status

Applicant respectfully requests reconsideration. Claims 76-78, 81, 86-88, 91, 108, 110, 112, 115-120 and 124-177 were previously pending in this application. Claims 112, 124-129, 156-157, 160-161, 164-165, 168-169, 172-173, and 176-177 are hereby canceled without prejudice or disclaimer. Applicant reserves the right to pursue the subject matter of the canceled claims in one or more continuing applications.

Claims 76, 78, 81, 86, 88, 91, 110, 115, 117-120, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, and 174 are amended herein. Claims 76, 78, 81, 86, 88, 91, 110, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, and 174 now recite that the isolated RNA consists of naturally occurring nucleotides; support for which is found in the specification at least at page 3, lines 6-8.

Claims 86, 88, 91, 142, 146, 150, 166 and 170 have been amended to recite that the isolated RNA is obtained from double-stranded RNA that has been enzymatically cleaved into fragments. Support for this amendment is found in the specification at least at page 11, lines 8-10; at page 35, line 15 to page 36, line 27; and in figure 11. Claims 154, 158, 162, 166, 170 and 174 have been amended to recite that the mRNA is a human cellular mRNA that encodes a protein whose presence in a human is associated with disease or undesirable condition. Support for this amendment is found in the specification at page 7, lines 24-29 and page 16, lines 3-14. Claims

115 and 117-120 have been amended to update claims dependencies in view of canceled claim 112.

As a result, claims 76, 77, 78, 81, 86-88, 91, 108, 110, 115-120, 130-155, 158-159, 162-163, 166-167, 170-171, and 174-175 remain pending for examination with claims 76, 77, 81, 86, 88, 91, 110, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, and 174 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claims 86-88, 91, 112, 115-120, 124, 126, 142-153 and 166-177 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that this is a new matter rejection. The Examiner asserts that adequate written description support is not found in the instant application for the entire genus of cleavage processes for producing isolated RNAs of 21-23 nucleotides from dsRNA.

Applicants respectfully disagree. However, in the interest of expediting prosecution, and without prejudice or disclaimer, Applicants have amended the claims to recite that isolated RNA is obtained from double-stranded RNA that has been "enzymatically cleaved" into fragments. Thus, the genus of cleavage processes for producing isolated RNAs of 21-23 nucleotides from dsRNA is no longer generic to any process for cleaving double stranded RNA as the Examiner had indicated.

The specification includes support for the limitation that the double-stranded RNA has been "enzymatically cleaved". In particular, Figure 11 of the specification, in part, depicts enzymatic cleavage of the dsRNA to produce 21-23 nt products. With reference to this figure, the specification states that "RNAi is envisioned to begin with *cleavage* of the dsRNA to 21-23 nt products by a dsRNA-specific *nuclease*, perhaps in a multiprotein complex." Specification at page 11, lines 8-10, emphasis added. The specification further provides, through working examples based on a drosphilia embryo lysate system that recapitulates RNAi *in vitro*, an inherent disclosure of enzymatic cleavage. As the Examiner is aware, by disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or

advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Using an *in vitro* system that recapitulates RNAi, the specification discloses that the processing of dsRNA leads to 21-23 nucleotide fragments in a manner that does not require target mRNA and that is sensitive to ATP levels. Specification at page 35, line 15 to page 36, line 27. Although Applicants do not explicitly state that the ATP-sensitive cleavage process involves RNAse III-like enzymatic activity, it inherently does, as evidenced by Elbashir et al. Using this same *in vitro* system Elbashir et al later reported that the 21-23 nucleotide fragments produced in the system possess a structure that is indicative of the fragments being generated by cleavage of the dsRNA by an RNAse III-like enzyme. Elbashir et al., Genes Dev. (2001) 15: 188-200. Berstein et al. have confirmed that the cleavage of dsRNA is mediated by the RNAse III enzyme Dicer. Berstein et al. Nature 409, 363-366 (18 January 2001). Notably, in the instant specification, Applicant propose a model for RNAi in which "the dsRNA is first cleaved to 21-23 nt long fragments in a process likely to involve genes such as the C. elegans loci rde-1 and rde-4". Specification page 40, lines 9-21. In C. elegans, RDE-4 is a dsRNA binding protein that forms a complex with the RNAse III enzyme DCR-1 (also referred to as dicer) and mediates cleavage of the dsRNA. Tabara et al., Cell 2002 Vol. 109, p861. Thus, Applicants appreciated at the time of filing that the process involving the lysate system was a protein mediated "cleavage process" and, although not specifically stated in the specification, this cleavage process involved digestion of the dsRNA by an RNAse III-like enzyme. Accordingly, the specification also provides inherent written description support for enzymatic cleavage of dsRNA to produce 21-23 nucleotide fragments.

In view of the foregoing, withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. 102

Claims 154-177 have been rejected under 35 U.S.C. 102(b) as being anticipated by Manche et al. (1992) *Molecular and Cellular Biology* 12:5238-5248, as evidenced by Stratagene

pBluescript II Phagemid Vectors Instruction Manual for Catalog #212207, downloaded from the Strategene, Inc. website on January 11, 2007, and a Basic Logic Alignment Search Tool (BLAST) analysis, available through NCBI, of nucleic acid sequence "cccggtacccagcttttgttccc" completed on January 11, 2007.

Applicants respectfully disagree. However, without conceding and solely in the interest of expediting prosecution, Applicants have amended the rejected claims to recite that the mRNA is human cellular RNA and encodes a protein whose presence in a human is associated with a disease or undesirable condition. The Office has identified putative targets having sequence correspondence with the double stranded RNA of Manche et al. None of the putative targets, based on the evidence provided by the Office, encodes human proteins associated with a disease or undesirable condition. Accordingly, Manche et al. do not disclose all of the limitations of the amended claims and, therefore, do not anticipate the claims.

In view of the foregoing, Applicants request reconsideration and withdrawal of the instant rejection.

Rejection Under 35 U.S.C. 103

Claims 76-78, 81, 86-88, 91, 108, 110, 112, 115-120 and 124-177 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Crooke et al. (US Patent 6,107,094), as evidenced by Tuschl et al. (US 20040259247 A1) and Amarzguioui et al. (2003) *Nucleic Acids Res.* 31:589-595.

Applicants respectfully disagree. However, without conceding and solely in the interest of expediting prosecution, Applicants have amended the rejected claims to recite that the isolated double-stranded RNA consists of naturally occurring nucleotides, *e.g.*, ribonucleotides, deoxyribonucleotides. As the Examiner acknowledges Crooke et al. teach chemically modified dsRNAs. Office Action at page 26, paragraph 3. Indeed, the 17 and 20 nucleotide dsRNA substrates of Crooke et al., (Table 1) have a sense strand consisting of an "oligoribonucleotide having phosphodiester linkages in an eight-base gap with flanks having either (a) residues with phosphorothioate linkages or (b) 2'-methoxynucleosides with phosphorothioate linkages" and an

antisense strand consisting of "2'-methoxy phosphorothioate wings on either side of an eight-base ribonucleotide gap having either phosphodiester or phosphorothioate linkages". Crooke et al., Example 27a, Column 50, lines 51-60. Applicant is not aware of a teaching that "2'-methoxy phosphorothioate nucleic acids are naturally occurring. Crooke et al. does not teach or suggest dsRNAs consisting of naturally occurring nucleotides as recited in the pending claims. Accordingly, Crooke et al., as evidenced by Tuschl and Amarzguioui does not teach or suggest all the limitations of the pending claims.

In view of the foregoing, withdrawal of the rejections is respectfully requested.

Double Patenting

Commonly Owned Application

Claims 76-78, 81, 86-88, 91, 108, 110, 112, 115-120 and 124-177 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17, 20-23, 76 and 80-85 of copending Application No. 10/255,568.

It is requested that the foregoing rejection be held in abeyance until allowable subject matter in the instant application is identified. At that time, Applicant will consider filing a terminal disclaimer.

Also, Applicant notes that claim 21 has been canceled in Application No. 10/255,568 rendering moot any rejection of the instant claims in view thereof.

Non-Commonly Owned Applications

Claims 76-78, 81, 86-88, 91, 108, 110, 112, 115-120 and 124-177 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30 and 34-55 of copending Application No. 11/142,866.

Claims 76-78, 81, 86-88, 91, 108, 110, 112, 115-120 and 124-177 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48, 49, 51, 53-57, 60-64, 67-73 and 75-125 of copending Application No. 10/433,050.

Applicant respectfully disagrees with the Examiner's position. However, it is requested that the foregoing rejections of the non-commonly-owned applications be held in abeyance until allowable subject matter in the instant application is identified. Because, in both cases, the instant application is the earlier filed application based on an earlier effective US priority date, it should be allowed to issue without the need of a terminal disclaimer, as provided in MPEP 804.I.*B.*1.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance. If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. W0571.70010US02.

Respectfully submitted,

Dated: September 9, 2009

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September 8, 2009

VIA E-MAIL

Mr. Martin Mullins
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Re: U.S. Patent Application No.: 09/821,832
Entitled: RNA Sequence-Specific Mediators of RNA Interference
Our Ref.: 2923-975

Dear Mr. Mullins:

We are writing on behalf of Max-Planck to respond to your letter of September 4, 2009, to Dr. Erselius concerning the above-identified US patent application. We only received today the decision from the PTO granting our Goldstein Petition, and assume that by now you have also received it. As such, we need to agree upon what paper will be acceptable for signing by both parties.

Max-Planck is willing to sign either of the following:

(i) a response that deletes from the application the priority claim to the EP application and the information received from the Tuschl II inventors; or

(ii) the papers necessary for a continuation application.

While we obviously prefer Option (i), Option (ii) would be acceptable to maintain the status quo.

Max-Planck is not willing to sign the proposed response because it does not delete the claim to the Tuschl II EP priority application, and does not delete from the application the information obtained from the Tuschl II inventors. The entire response is defective in that the PTO has made it clear that it is relying on the entire contents of the application in examining the claims. In addition, the entire discussion of inherency in the response from page 13, line 6

through page 14, line 8, is a violation of the agreement that the Tuschl II applications have the exclusive right to claim 3' overhangs.

Finally, the requests on page 16 that the double patenting rejections should be withdrawn and only applied against the Tuschl II applications is unacceptable. The double patenting rejections are the result of the application claiming subject matter that should only be claimed in Tuschl II applications, and as such, any response would need to have claims that are supported by the application after the priority claim and Tuschl II inventor information have been deleted.

We look forward to receipt of the papers you propose to file for our review, and if they are acceptable, our signature.

Sincerely,

Robert B. Murray

RBM/cb